Objectives: To summarize the quality of evidence for the efficacy of different biological treatments in mania, mixed state, and rapid cycling and to propose guidelines for treatment of these conditions.

Method: Articles published on treatment of acute mania, mixed states, and rapid cycling were reviewed and rated for quality of evidence using Periodic Health Examination guidelines.

Results: Lithium and divalproex sodium are effective in classical pure mania, whereas divalproex sodium and carbamazepine are likely more effective in mixed states. Divalproex sodium is likely more efficacious than carbamazepine and lithium when the mania is part of a rapid-cycling course. Typical neuroleptics are efficacious in acute mania, particularly in the presence of marked psychotic symptoms. Atypical neuroleptics can be useful in refractory mania. Some benzodiazepines do have antimanic effects, but they are increasingly being shown to have usefulness as adjuncts to mood stabilizers or neuroleptics rather than as primary antimanic agents. Electroconvulsive therapy (ECT) is an efficacious and broad-spectrum treatment.

Conclusions: Mania can present with or without mood-congruent or mood-incongruent psychotic features and as part of a rapid-cycling or nonrapid-cycling course. Mixed state is a common presentation in an acutely manic patient. The accurate assessment of these issues can serve as a guide in determining treatment options and choices.

Key Words: mania, mixed state, rapid cycling, lithium, divalproex sodium, carbamazepine, neuroleptics, benzodiazepines, electroconvulsive therapy
There is considerable evidence that sleep deprivation can provoke mood destabilization, particularly mania (7). Normalization of both the quantity of sleep and biorhythms can be useful in the prevention of mood instability and as an adjunct to mood stabilizers in the treatment of hypomania and mania.

Medical Evaluation of New Patients

Ideally, a medical evaluation and baseline investigations should be completed before the institution of biological treatment. In certain circumstances, however, because of a very acute clinical situation, treatment may have to begin prior to the completion of a medical evaluation and investigations.

Apart from a thorough medical examination, the following baseline investigations should be completed: complete blood count including platelets and electrolytes; liver enzymes and serum bilirubin, prothrombin time and partial thromboplastin time; urinanalysis and urine toxicology for substance use; serum creatinine, and if there is any personal or family history of renal disease, a 24-hour creatinine clearance; thyroid-stimulating hormone; electrocardiogram for patients over 40 years or if indicated otherwise; pregnancy test if relevant.

During the acute phase, aim for the following serum levels: lithium 0.8 to 1.1 mmol/L; valproic acid 400 to 700 mmol/L; for carbamazepine, there is no proven therapeutic level. Note that lithium can be given in a single dose, as can slow-release carbamazepine, but divalproex should be given in 2 divided doses daily because of the absence of data on single daily dose treatment.

Serum levels should be repeated at the trough point (approximately 12 hours after the last dose). For lithium, serum levels can be done about 5 days after most recent dose titration; for divalproex and carbamazepine, about 3 to 5 days after the most recent dose titration. Common practice is to establish about 2 consecutive serum levels in the therapeutic range during the acute phase. Thereafter, serum levels can be repeated every 3 to 6 months unless the clinical situation warrants otherwise.

There is no evidence that blood counts and liver functions need to be done frequently (8,9). These investigations should be repeated about 4 weeks after commencement of treatment, and could be repeated once every 3 to 6 months thereafter. Closer monitoring, however, is required in children below the age of 10, seniors, medically ill patients, and patients on more than one medication. Clinical symptoms and signs of hematological, hepatic, cardiovascular, and neurological dysfunc-

tion are particularly valuable in predicting or timing investigations and remedial treatment (8,9). Thyroid and renal functioning, for lithium users, needs to be assessed annually. More extensive investigations should be performed only if there is a clinical indication.

### Table 1. Quality of evidence and recommendations for treatments:
acute mania, mixed state, and rapid cycling

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Quality of evidence</th>
<th>Working group classification of recommendation</th>
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<tbody>
<tr>
<td>Acute mania</td>
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<tr>
<td>Lithium</td>
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<td>A</td>
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<tr>
<td>Divalproex</td>
<td>1</td>
<td>A</td>
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<tr>
<td>Carbamazepine</td>
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<td>B</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Gabapentin</td>
<td>na</td>
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<tr>
<td>Typical neuroleptic</td>
<td>1</td>
<td>C±</td>
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<tr>
<td>Atypical neuroleptic</td>
<td>2.3</td>
<td>B</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>ECT</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>Lorazepam</td>
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<tr>
<td>Mixed state</td>
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<tr>
<td>Lithium</td>
<td>1</td>
<td>C</td>
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<tr>
<td>Divalproex</td>
<td>1</td>
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<tr>
<td>Carbamazepine</td>
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<td>B</td>
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<tr>
<td>Lamotrigine</td>
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<tr>
<td>Gabapentin</td>
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<tr>
<td>Typical neuroleptic</td>
<td>3</td>
<td>D</td>
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<tr>
<td>ECT</td>
<td>3</td>
<td>C</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>3</td>
<td>D</td>
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<tr>
<td>Rapid cycling</td>
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<tr>
<td>Lithium</td>
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<td>C</td>
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<tr>
<td>Divalproex</td>
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<td>Carbamazepine</td>
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<td>Gabapentin</td>
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<tr>
<td>Lorazepam</td>
<td>3</td>
<td>D</td>
</tr>
</tbody>
</table>

aQuality of evidence rating system:
1 At least one randomized controlled trial.
2.1 Well-designed controlled trial without randomization.
2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees.

bClassification of recommendations:
A Good support for the intervention to be considered in clinical practice.
B Fair support for the intervention to be considered in clinical practice.
C Poor support for the intervention to be considered in clinical practice.
D Fair support for the intervention to be excluded from clinical practice.
E Good support for the intervention to be excluded from clinical practice.

Despite the proven antimanic efficacy of typical neuroleptics, the working group was of the opinion that they should not be considered the sole or primary antimanic agents except in exceptional circumstances in view of the high risk of tardive dyskinesia with long-term use in this population.
Pharmacological Treatment of Acute Classical Pure Mania and Mixed State, with or without a Rapid-Cycling Course

The quality of evidence for different treatments as assessed by the Periodic Health Examination classification is presented in Table 1. Treatment recommendations for acute mania, mixed state, and rapid cycling are discussed below and illustrated in algorithms (10), reproduced courtesy of the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Figures 1 and 2).

**Lithium**

Lithium has been shown to be superior to placebo and comparable in efficacy to antipsychotic and anticonvulsant agents (11–20). Pooled response rates from double-blind, placebo-controlled studies of lithium and acute mania showed significant improvement in 70% of patients. Bowden and others (13) demonstrated that 49% of patients treated with lithium displayed at least a 50% reduction in manic symptoms over a 3-week period. No other psychotropic medications were permitted in this study except the use of lorazepam as needed up to 4 mg/day and restricted wherever possible to the initial phase of treatment. The consensus is that lithium is superior to antipsychotics or benzodiazepines in normalizing the affective symptoms but that neuroleptics have a more rapid onset of action and therefore may be more effective in the initial treatment of acute mania and in the acutely agitated patient (21–23). Failure to respond to lithium is associated with both the presence of a mixed state as well as a rapid-cycling current course of which the acute mania is a part (24–31). The presence of depressive symptoms during mania or immediately preceding mania may be predictive of response to divalproex and nonresponse to lithium (32) (Table 2).

**Divalproex Sodium**

Divalproex sodium and valproate have been shown to be effective in the treatment of acute mania in placebo crossover trials (33) and compared with lithium and placebo in a randomized parallel-group trial (34). Divalproex sodium is preferred in clinical practice because it has fewer gastrointestinal side effects than sodium valproate or valproic acid. Bowden and others reported that divalproex was as effective as lithium and both were significantly better than placebo in the treatment of acute mania (13). Compared with the limited effect produced by lithium in rapid-cycling bipolar type I disorder patients, divalproex was effective in these patients in addition to those who had a nonrapid-cycling course. As previously mentioned, in Bowden and others’ study (13), no other psychotropic medications were used other than lorazepam up to 4 mg/day as an adjunct to both interventions, primarily during the initial phase of treatment. The effectiveness in clinical
practice would be expected to be enhanced by the use of adjunctive agents like benzodiazepines or neuroleptics. Divalproex sodium is effective in rapid-cycling patients as well as in more than 50% of patients in a mixed state. The presence of depressive symptoms during mania or immediately preceding a manic episode may be predictive of response to divalproex and nonresponse to lithium (32) (see Table 2). Although clinicians have commonly justified the use of neuroleptics because of their early onset of action, there is growing evidence that oral loading doses of 15 to 20 mg/kg/day of divalproex can produce rapid onset of antimanic action comparable to that of haloperidol but with fewer side effects (35).

**Carbamazepine**

There are numerous double-blind studies to support the efficacy of carbamazepine in the treatment of acute mania (36–42). The majority of these studies, however, are confounded by the concurrent administration of antipsychotics and/or lithium (43). This is important to note because there is reported synergistic action when carbamazepine and lithium are combined in situations where patients fail to respond to either medication on its own (44). Pooled data support that the overall response rate of 50% in the treatment of acute mania is no different from that for divalproex sodium and lithium (45) (see Table 2). Carbamazepine is reportedly effective in mixed state, but its value in rapid cycling is being increasingly questioned (46).

**Lamotrigine and Gabapentin**

There is insufficient evidence at this stage with both lamotrigine and gabapentin to support their efficacy as first-line agents in acute pure mania. There are case reports and small case series, however, that support the value of lamotrigine in rapid-cycling states (47). Controlled double-blind studies with both compounds are currently under way. At present, these compounds are used only in refractory mania, mixed states, or rapid cycling.

**Benzodiazepines**

Lorazepam and clonazepam have been the most studied benzodiazepines in acute mania, and controlled studies support the conclusion that both agents are useful in the treatment of acute mania (48–52). Bradwejn and others, in a double-blind comparison of the effects of clonazepam and lorazepam in acute mania without the use of other psychotropic agents over a 14-day period, reported that 61% of patients responded positively to lorazepam treatment, with 38.5% achieving remission (48). This compared with only an 18.2% response rate and a 0% remission rate in patients treated with clonazepam alone. Clinicians have raised concerns about the possibility of exacerbating disinhibition in acute mania with the use of benzodiazepines on their own, but they have been shown to be useful adjuncts with mood stabilizers in the treatment of acute mania (52,53). Bowden and others demonstrated the efficacious use of lorazepam as an adjunct for behavioural suppression when used with either lithium or divalproex (13).

Collectively, studies suggest that benzodiazepines are effective in place of or in conjunction with a neuroleptic in sedating the acutely agitated manic patient while waiting for the effects of other primary mood-stabilizing agents to become evident. Lorazepam has, by virtue of its multiple routes of administration and favourable intramuscular absorption, become a useful choice. Further, both lorazepam and clonazepam are preferable to neuroleptics if the possibility of precipitating extrapyramidal symptoms and acute dystonias is unacceptable. An obvious disadvantage of benzodiazepines are their propensity for dependence and, in patients with comorbid substance use disorder, the potential to induce another substance use disorder is a cause for concern. Benzodiazepines also have the potential to cause either dysphoria or disinhibition in some patients (54,55).

**Typical Neuroleptics**

Controlled studies have shown that neuroleptics are superior to placebo in the treatment of acute mania (23). Studies comparing lithium with neuroleptics (chlorpromazine or haloperidol) usually suggest that, while lithium may be superior to neuroleptics for the specific normalization of mood, neuroleptics often have a quicker onset of action (17,19,23,56–61).

Although clinicians have commonly justified the use of neuroleptics because of their early onset of action, there is growing evidence that oral loading doses of 15 to 20 mg/kg/day of divalproex can produce rapid onset of antimanic action and an antipsychotic response comparable to that of haloperidol but with fewer side effects (35). Neuroleptics carry the risk of causing extrapyramidal symptoms and acute dystonia, as well as an increased risk of tardive dyskinesia with long-term use in patients with a mood disorder.

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**Table 2. Predictors of response or nonresponse for 3 treatments**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Predictors of response</th>
<th>Predictors of nonresponse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Acute mania</td>
<td>Mixed state</td>
</tr>
<tr>
<td></td>
<td>Family history of response</td>
<td>Depression–mania–euthymia course</td>
</tr>
<tr>
<td></td>
<td>Mania–depression–euthymia course</td>
<td>Rapid cycling</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder, 3 or fewer cycles per year</td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Acute mania</td>
<td>Rapid cycling</td>
</tr>
<tr>
<td></td>
<td>Mixed state</td>
<td>Mixed state</td>
</tr>
<tr>
<td></td>
<td>Secondary mania</td>
<td>Rapid cycling</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Acute mania</td>
<td>Rapid cycling</td>
</tr>
<tr>
<td></td>
<td>Mixed state</td>
<td>Secondary mania</td>
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</tr>
</tbody>
</table>
Atypical Neuroleptics

Both risperidone and clozapine have antimanic properties as reported by a variety of investigators in uncontrolled studies (23,62–70). Calabrese and others demonstrated in an open trial that clozapine was effective in both pure bipolar disorder and in mania related to schizoaffective disorder that was resistant to front-line antimanic treatments (71). Despite the difficulty in obtaining clozapine for patients without schizophrenia in many provinces in Canada and the risk of hematological side effects, there is growing evidence that clozapine may be an appropriate mood-stabilizing agent in refractory mania. This intervention may also have a role in the treatment of refractory bipolar depression (65,70,72).

The interpretation of studies of risperidone use in acute mania are complicated by the inclusion of patients with bipolar disorder who were already receiving mood stabilizers. The dose of risperidone in these studies varied from 1 to 6 mg/day. There are some data to suggest that risperidone, especially when given in higher doses of 6 to 8 mg/day, may induce or exacerbate manic symptoms (73). Systematic studies are under way with this compound in acute mania.

The thymoleptic role of other atypical neuroleptics, such as olanzapine and sertindole, remains uncertain at this time. Preliminary data on olanzapine suggest that it may have antimanic and antidepressant properties in addition to its antipsychotic effects.

ECT

In a review of ECT in acute mania, Mukherjee and others found that 80% of patients showed marked clinical improvement (74). Many manic patients respond relatively rapidly to ECT when compared with their response to mood stabilizers (75). The attractiveness of ECT is also that patients who are treatment-refractory to pharmacotherapy often respond to ECT (76). There is little evidence that manic patients require a high frequency or prolonged course of treatments to respond to ECT. The seizure threshold appears to be lower in manic patients than in depressed patients. The majority of studies reviewed by Mukherjee and others reported that bilateral ECT was superior to unilateral ECT in the treatment of acute mania (74). This issue requires further study, although clinical consensus appears to be that bipolar patients do better with bilateral ECT. The presence of pregnancy, manic delirium with severe hypothermia, neuroleptic malignant syndrome, catatonia, and some comorbid general medical conditions may be primary indications for ECT, both in view of its effectiveness and its high margin of safety in these situations (77). Despite a lack of rigorous studies, clinical experts agree that ECT is useful both in rapid-cycling and mixed state illness as well as in refractory states with these conditions. Lithium should be temporarily discontinued or the dosage dramatically reduced when using ECT to avoid the rare but potentially fatal associated complications of delirium and status epilepticus (78–80). Benzodiazepine and anticonvulsant administration should be minimized or discontinued briefly to optimize seizure duration and threshold (81).

Calcium Channel Blockers and Thyroxine

Bowden has stated that the studies with calcium channel blockers are small in number, flawed in design, and mixed in results (82). Although in initial studies verapamil was reported to be superior to placebo (83,84), the only randomized placebo-controlled study reported no differences in outcome between verapamil and placebo treatment (85). In addition, one study has shown that verapamil may worsen or precipitate depression (86). Verapamil is weakly lipophilic and probably does not reach the central nervous system in adequate concentrations. Several other calcium channel blockers are highly lipophilic, and nimodipine, a dihydropyridine that blocks the calcium channel directly, has been reported to be efficacious in small case series of rapid-cycling patients, particularly the ultrarapid-cycling variety. There is no conclusive evidence of the value of thyroxine supplementation in rapid-cycling disorder except where there is proven hypothyroidism.

Psychotic Mania

Available studies indicate that mood-congruent grandiose delusions are probably the most common type of psychotic symptoms in mania (87). Mood-incongruent psychotic symptoms are also commonly seen in acute mania (87,88). Psychotic symptoms appear to be commonly associated with increasing severity of an acute manic episode. McElroy and others (23) and Tohen and colleagues (89) conclude that there is inconsistent evidence as to whether psychotic mania is associated with a similar or poorer outcome compared with nonpsychotic mania. There is no conclusive evidence to suggest that mood-incongruent or bizarre psychotic symptoms and formal thought disorder are associated with poorer outcome when seen in acute mania. Persistent psychotic symptoms present in the continuation and maintenance phases of the illness, however, are associated with relatively poorer prognosis. No controlled study has prospectively examined the response of patients with acute mania to antipsychotics, mood stabilizers, or an antipsychotic plus mood stabilizer combination according to the presence or absence of psychotic symptoms.

It is unknown, therefore, whether patients with psychotic mania truly require adjunctive neuroleptics for optimal response more often than those patients with nonpsychotic mania (23). A second issue is that typical antipsychotics may exacerbate bipolar depressive symptoms both acutely and over the long term (90–94). Limited evidence suggests that the newer atypical neuroleptics do not provoke bipolar depression.

Common practice has been to treat acute psychotic mania, especially if accompanied by severe agitation, with neuroleptic medication initially, in order to hasten and maximize the
treatment response. Preliminary studies suggest that benzodiazepines may be as effective as neuroleptics in reducing agitation when used adjunctively with a mood stabilizer to treat acute mania (51). Further, oral loading with divalproex sodium (15 to 20 mg/kg/day) may produce rapid onset of an antimanic and antipsychotic response comparable to that of haloperidol and with minimal side effects in the initial treatment of acute psychotic mania in some bipolar patients (35). The use of oral loading with divalproex, which may have an early onset of action superior to lithium, may obviate the need for antipsychotic medication treatment in many instances. As reported earlier, the newer typical neuroleptics like risperidone and clozapine have also been reported to be useful in patients refractory to traditional mood stabilizers, although risperidone in doses above 6 mg may exacerbate mania.

In summary, neuroleptic medications offer advantages and disadvantages. Advantages include early onset of action, parenteral administration in patients refusing oral medication, specific antipsychotic effects in patients with persistent psychotic symptoms, and clinical familiarity with their use. The disadvantages and limitations include extrapyramidal symptoms, acute dystonias, tardive dyskinesia seen with typical neuroleptics, hematological complications with clozapine, and the possibility of exacerbation of mania with doses of risperidone over 6 mg/day.

Although inconsistencies exist, considerable data suggest that neuroleptic treatment in acute mania with psychosis, in general, is not associated with better outcome. McElroy and others have stated that the acute and maintenance treatment of psychotic mania should be similar to that of nonpsychotic mania, with mood stabilizers being the primary agents (23). Typical neuroleptics should be reserved for patients with severe acute agitation, those who refuse oral medication, those who present mood-incongruent or persistent psychotic symptoms, and those who are inadequately responsive to, intolerant of, or noncompliant with mood stabilizers. By contrast, atypical neuroleptics like risperidone and clozapine, both of which need to be studied further, may be superior choices to typical neuroleptics in acute psychotic mania and refractory mania.

Summary of Evidence and Recommendations

Table 1 summarizes the quality of available evidence (using the Periodic Health Examination classification) for the treatment of acute mania, mixed state, and rapid cycling, as well as the classification of recommendations of the working group for use in clinical practice. The classification of recommendations is the product of a consensus process and reflects a global impression based on the quality of evidence for efficacy, adverse effects, tolerability, and acceptability for the patient.

Treatment of Acute Mania and Mixed States (see Figure 1)

In acute mania, it is common practice to begin treatment with a mood stabilizer, either lithium or divalproex. In mixed mania, divalproex and carbamazepine are the drugs of choice. The principle is to use the medication that has antimanic efficacy and is likely to be used for prophylaxis. In moderate to severe mania, there is often a need to achieve rapid stabilization. This can be accomplished by the use of a loading dose of 20 mg/kg/day of divalproex, the use of lorazepam or clonazepam in doses from 2 to 12 mg/day, and/or, where there is severe behavioural disturbance and marked psychosis, the use of a neuroleptic or ECT. Both typical and atypical neuroleptics have specific antimanic effects. Neuroleptics should be discontinued after the patient has been stabilized, usually about 2 weeks into treatment unless there are persistent and/or mood-incongruent psychotic symptoms. Behaviour suppressors like lorazepam and clonazepam have been used successfully as adjuncts instead of neuroleptics (53). Neuroleptic use is indicated in the long term if there is persistent or mood-incongruent psychosis. In such cases, it is important to taper and stop antidepressants or other maniogenic agents and to stabilize sleep patterns. Substance and alcohol use should be discontinued.

If the mania or mixed state is refractory to treatment, there should be a reassessment of the possibility of an underlying treatable medical cause. Any medical condition or substance abuse should be treated. If these are not present, the clinician may add a second mood stabilizer while concurrently evaluating the need for ECT, depending on the clinical situation. The combination of 3 mood stabilizers (lithium, divalproex, and carbamazepine) and an atypical neuroleptic (risperidone, in doses below 4 mg/day, or clozapine at therapeutic doses) may be tried sequentially. The addition of a calcium channel blocker or a novel agent like lamotrigine or gabapentin may also be considered.

It is usually sufficient to measure serum medication levels no more frequently than once a week in the acute phase. Serum medication levels should be repeated until 2 consecutive levels have been obtained in the therapeutic range. After baseline investigations, the monitoring of bodily systems should be conducted as clinically indicated.

Treatment of Rapid-Cycling Bipolar Disorder (see Figure 2)

Rapid-cycling bipolar disorder may be a phase of the disorder or, in some cases, a type of disorder. It is important to stabilize sleep and to reduce or stop the use of caffeine, nicotine, alcohol, and other substances. Antidepressant medications, particularly tricyclics, may provoke rapid cycling. Care should be taken to discontinue any psychotropic agents gradually, never abruptly.

Divalproex sodium is the first treatment of choice. In partial or nonresponders, lithium or carbamazepine may be added to the divalproex. Further on, the combination of 3
mood stabilizers or ECT could be tried. Lamotrigine, gabapentin, nimodipine, or thyroxine in addition to an established mood stabilizer may be used. Clozapine should be considered in the truly refractory patient.

Clinical Implications

- Although lithium is a tried and tested medication with proven efficacy in acute mania, divalproex sodium likely has a broader-spectrum efficacy, and carbamazepine can be an alternative in certain clinical situations.
- There are important but limited roles for neuroleptics, benzodiazepines, and ECT.

Limitations

- The evidence from well-designed, double-blind controlled studies with adequate numbers of patients is mainly limited to lithium and divalproex.
- There are no methodologically sound studies in mixed state and rapid cycling.
- There is sparse evidence for the efficacy of atypical neuroleptics and novel agents.

References


Résumé

Objectifs : Dresser un sommaire de la qualité des résultats relatifs à l’efficacité de divers traitements biologiques de la manie, de l’épisode mixte et des cycles rapides et proposer des lignes directrices pour traiter ces pathologies.


Résultats : Le lithium et le divalproex sodique sont efficaces en cas de manie pure et classique, alors que le divalproex sodique et la carbamazépine sont probablement plus efficaces en cas d’épisodes mixtes. Le divalproex sodique est sans doute plus efficace que la carbamazépine et le lithium quand la manie fait partie d’une évolution à cycles rapides. Les neuroleptiques typiques peuvent être utiles en cas de manie aiguë, en particulier en présence de symptômes psychotiques prononcés. Les neuroleptiques atypiques peuvent être utiles en cas de manie réfractaire. Certaines benzodiazépines provoquent vraiment des effets antimaniaco-dépressifs, mais les preuves s’accumulent quant à leur utilité en accord avec les psychorégulateurs ou aux neuroleptiques et non pas principalement comme des agents antimaniaco-dépressifs. L’électrochoc constitue un traitement efficace et polychаn.